REMARKS

Prior to the present amendment, claims 1, 2, 11, 12, and 34-36 were pending. By the present amendment, applicants have amended claims 1 and 36 and cancelled claim 35. Accordingly, claims 1, 2, 11, 12, 34, and 36 are currently pending.

Support for the amendments to claims 1 and 36 can be found in the specification as filed on page 4, lines 27-29; page 5, lines 2-5; and claim 1 as originally filed. Accordingly, no new matter has been entered by the amendments to the claims.

INTERVIEW

Applicant wishes to thank Examiner Leslie A. Royds and her supervisor, Supervisory Patent Examiner Ardin H. Marschel for taking the time to discuss the office action dated March 11, 2009 with his representatives, Linda D. Chin and the undersigned. Dr. Runzhi Zhao, in-house counsel at Galderma, the assignee, and technical expert, Dr. Guy Webster also participated in the interview. Applicant's representatives discussed the 35 U.S.C. 103 rejection with the examiners. The discussion below contains a summary of the interview.

35 U.S.C. 103 REJECTION

In her office action dated March 11, 2009, Examiner Royds rejected claims 1-2, 11, 12, and 34-36 under 35 U.S.C. 103(a) as being unpatentable over Wymenga, et al. ("Management of Hot Flushes in Breast Cancer Patients," *Acta Oncologia*, 41(3); 2002:269-275) in view of U.S. Patent Publication No. 2003/0229088 to Gil, et al., Burke, et al. ("Preclinical Evaluation of Brimonidine," *Survey of Ophthalmology*, 41(Supp.1), 1996, S9-S18) and Dictionary.com ("Topical" and "Transdermal," 2008).

Applicant has responded to this rejection in the previous response dated December 9, 2008. The examiner is respectively requested to review this response, since applicant believes

that it adequately addresses all of the points raised by the examiner in her previous office action, dated June 10, 2008.

During the interview, applicant's representatives pointed out disagreements they have with some of the statements made in the "Response to Applicant's Arguments" section of the Office Action. These disagreements are summarized below.

At page 7, starting at line 14, the examiner states:

> …transdermal application results in absorption of the active agent into the bloodstream and, thus, distributes the agent throughout the body via the blood. This same distribution throughout the body as a whole clearly supports the interpretation that the agent would act "locally," as instantly claimed, at the site of the facial flushing to exert its selective alpha-adrenergic receptor agonist activity once it has been distributed to this site of the skin via the bloodstream, absent factual evidence to the contrary. (emphasis added)

Applicant does not agree with the examiner's statement that transdermal administration acts locally. In particular, the following definitions appear in Dorland's Illustrated Medical Dictionary 2003 Ed. (relevant pages submitted herewith in a Supplemental Information Disclosure Statement):

local: restricted to or pertaining to one spot or part; **not general**

systemic: pertaining to or affecting **the body as a whole**

(Emphasis added, see pages 1065 and 1848, respectively.)

According to Dorland's, the word "local" pertains to one part of a body. By contrast, the word "systemic" pertains to the body as a whole.

The examiner acknowledged in the office action that "transdermal application results in absorption of the active agent into the bloodstream." Therefore, transdermal administration is a form of systemic administration, since, as was also acknowledged by the examiner, it "distributes the agent throughout the body via the blood."

Applicant's representatives explained during the interview that the word "local" is the antithesis of the word "systemic" in the context of administration of a drug. Accordingly, the administration of a drug locally to the skin of a human, as presently claimed, is the antithesis of the administration of a drug systemically to the skin of a human, as disclosed in the Wymenga reference.

During the interview, Dr. Webster, applicant's technical expert, provided further evidence regarding the definitions of local and systemic administration. In particular, Dr. Webster confirmed that, to a person having ordinary skill in the art, local administration means an active agent affects only the area to which it is applied.

Dr. Webster also confirmed the examiner's understanding that transdermal administration, in contrast, is a form of systemic administration. In systemic administration, the active compound enters the bloodstream and is distributed throughout the body. (See the declaration of Dr. Webster submitted herewith.)

Examiner Marschel indicated his concern that the claims do not limit the scope of the administration to local administration. The undersigned noted that in a previously submitted response, evidence from the clinical trial of brimonidine tartrate was submitted to show that brimonidine tartrate does not enter the bloodstream in significant amounts.

During the interview, the undersigned could not locate the date the information was submitted. However, after reviewing the file, the undersigned would like to direct the examiner's attention to the clinical trial data submitted in a Supplement Information Disclosure Statement

filed on February 21, 2008 and the response filed on February 21, 2008, the paragraph bridging pages 6 and 7, which explains the data from the clinical trials.

The clinical trail data relates to a human study of the bioavailability of COL-118, *i.e.*, brimonidine tartrate, administered topically in a facial gel. Sixteen subjects (males and females between the ages of 18 and 55) were studied.

On page 4 of the study, it was noted that, after topical administration of the brimonidine gel to the faces of the subjects, plasma levels of brimonidine for all subjects were below the limit of quantification. On page 5 of the study, in the conclusions section, it is noted that "no exposure to brimonidine in the plasma was observed after facial administration of 0.2% (2mg brimonidine) COL-118 gel…"

Accordingly, applicant emphasizes that the claimed invention is directed to local administration of brimonidine wherein the brimonidine does not enter the blood in clinically significant amounts. In contrast, Wymenga discloses transdermal administration of clonidine wherein the clonidine acts centrally, *i.e.*, enters the bloodstream and crosses the blood-brain barrier. See Wymenga, page 271, first sentence of last paragraph.

Applicant understands the examiner's position to be that the efficacy of transdermal administration of clonidine for the treatment of menopausal flushing would lead a person having ordinary skill in the art to believe that there is a reasonable expectation that local administration of brimonidine would also be effective. Applicant's position is that there is too much unpredictability for any such expectation of success to be reasonable.

As will be demonstrated below, a person having ordinary skill in the art would not reasonably predict efficacy for the claimed reduction of menopausal flushing by the administration of brimonidine from the disclosure of efficacy for reducing menopausal flushing by the administration of clonidine, even if the mode of administration of brimonidine and of clonidine were the same. Such unpredictability is greatly magnified by the disclosure that the

administration of clonidine was systemic, while, by contrast, the claimed administration of brimonidine is local.

Simply stated, one cannot predict the effect of the local administration of a drug from the systemic administration of the same drug, to say nothing of a different drug. For example, one would not reasonably expect to be able to reduce the discomfort of a headache by formulating aspirin in a cream, and rubbing the composition on one's forehead. (See declaration of Dr. Guy Webster.)

At page 5, starting at line 4 of the office action, the examiner states the following:

> The prior art at the time of the instant invention clearly and explicitly acknowledged that the two compounds (i.e., clonidine and brimonidine) share the same overall function as alpha-adrenergic agonist and, thus, are "functionally equivalent" for this purpose.

It is true that clonidine and brimonidine are both classified as alpha-adrenergic receptor agonists. Applicant denies and the examiner does not assert, however, that clonidine and brimonidine are necessarily functionally equivalent with respect to the differences in their therapeutic function. Since applicant is claiming a medical treatment, applicant believes the relevant issue to be whether clonidine and brimonidine are reasonably expected to be therapeutically functionally equivalent, even if both are categorized as alpha-adrenergic receptor agonists. As applicant will demonstrate later, they are not.

At page 5, starting at line 6, the examiner states:

> The very fact that the two compounds may exhibit differing function in treating, e.g., redness associated with rosacea (i.e., that clonidine is ineffective for treating redness due to rosacea, while brimonidine is

> apparently effective for treating the same), does not negate this clear teaching that the two compounds fundamentally act as agonists of alpha-adrenoreceptors, wherein, according to Wymenga et al., agonism at such alpha-adrenoreceptors is effective for reducing facial flushing resulting from menopause-associated hot flashes. (emphasis added).

As mentioned above, the examiner is correct in stating that clonidine and brimonidine both act as alpha-adrenoreceptor agonists. This statement would be relevant if applicant was claiming a method of agonizing alpha-adrenoreceptors. Applicant is, however, not claiming such a method.

Instead, applicant is claiming a method of reducing cutaneous facial flushing caused by menopause-associated hot flashes. Applicant respectfully submits that the examiner has not made out a *prima facie* case that, prior to the present invention, a person having ordinary skill would understand that clonidine and brimonidine are therapeutically equivalent for the claimed purpose.

It is true that Wymenga discloses that "… clonidine appeared effective in the reduction of flushes caused by normal menopause or by surgical castration, either when administered orally or transdermally." See the paragraph bridging pages 271 and 272 at page 271, lines 3-6. However, Wymenga does not disclose that any other alpha adrenergic receptor agonist would be so effective, and certainly not that all other agonists, *e.g.*, brimonidine, would be effective.

Applicant considers it significant that Wymenga does not even disclose that agonizing alpha adrenergic receptors by clonidine is a mechanism of action in its efficacy in reducing menopausal flushes. In fact, there is evidence that clonidine is not acting by agonizing alpha adrenergic receptors.

In particular, agonists of alpha-adrenoreceptors typically cause a reduction in blood pressure. In the same paragraph that discloses oral or transdermal clonidine to be effective in reducing flushes caused by normal menopause, however, Wymenga also discloses that in a study of the effect of oral clonidine on flushing in breast cancer patients, "[n]o effect on blood pressure was reported." See page 271, col. 1, lines 19-20. See also the declaration of Dr. Guy Webster.

For all the above reasons, a person having ordinary skill would not be able to predict whether or not brimonidine would be effective in the reduction of flushes caused by normal menopause.

From the statement above (and elsewhere in the office action), it appears to be the examiner's hypothesis that all alpha-adrenergic receptor agonists predictably have the same therapeutic effect. Applicant provides factual evidence below that such predictability does not exist.

For example, it is known that the alpha-adrenergic receptor agonist brimonidine is effective to treat rosacea. If the examiner's hypothesis were correct, one would predict that another alpha-adrenergic receptor agonist, *e.g.*, clonidine, would also be effective to treat rosacea. However, clonidine has been reported to be ineffective in treating rosacea.

As further evidence that how a particular alpha-adrenoreceptor will function is unpredictable, applicant directs the examiner's attention to an article by Shanler, et al. in Arch. Dermatol. 143, 1369-1371 (2007), which is provided herewith. Shanler, et al. state:

> The current model is that of a complex family of structurally related receptors consisting of at least 6 α-receptor subtypes …
>
> … Their final local and systemic effects, however, are myriad, as noted previously, including vasoactive effects ranging from

> vasoconstriction to vasodilation, and occur through a wide variety of intracellular mechanisms.

See page 1370 of Shanler, et al., column 2, the last sentence of the first full paragraph and the second sentence of the next paragraph.

Accordingly, Shanler, et al. support the unpredictability in the art regarding how a particular alpha-adrenoreceptor agonist will affect a particular blood vessel, etc.

Furthermore, during the interview Dr. Webster agreed with Shanler, et al.'s conclusion that it is difficult to predict how a certain alpha-adrenoreceptor subtype will affect a particular part of the body. Dr. Webster uses the analogy that each alpha-adrenoreceptor subtype is like an electrical switch. Each switch can be turned on or off by an agonist or antagonist. However, the effect of turning on or off one adrenoreceptor subtype may not be the same as the effect of a turning on or off a different receptor subtype.

Moreover, the effect of an agonist or antagonist on an adrenoreceptor subtype in one part of the body may not be the same as the effect of an agonist or antagonist on the same adrenoreceptor subtype in a different part of the body. Such differing, indeed antithetical, effects are acknowledged in the Gil, et al. reference cited by the examiner. Thus, Gil, et al. state:

> The present invention is based on the surprising discovery that, in contrast to the pro-analgesic function of the α-2A receptor in the spinal column, a peripheral α-2A receptor mediates pain.

See Gil, et al. at paragraph 41. In other words, Gil, et al. report that an α-2A receptor in the spinal column eases pain, while a peripheral α-2A receptor causes pain.

It is clear that agonizing an alpha-adrenoreceptor may cause various unpredictable effects, such as vasodilation or vasoconstriction, that depend on the subtype of an adrenoreceptor

as well as on its location in the body. The effects of an alpha-adrenoreceptor subtype can be very different from that of another alpha-adrenoreceptor subtype, indeed the opposite, depending on the subtype and location in the body. (See the declaration of Dr. Webster submitted herewith.)

On page 6 of the office action, starting at page 6, line 7, the examiner states:

> …Gil et al. *further discloses that brimonidine and clonidine are functionally equivalent in their activity as alpha-adrenergic agonists*" (original emphasis).

It is true that Gil et al. disclose both brimonidine and clonidine to be effective in treating pain. It is also true, however, that both brimonidine and clonidine are not effective in reducing redness associated with rosacea, *i.e.*, brimonidine is and clonidine is not. Therefore, efficacy of both brimonidine and clonidine in treating one condition, *e.g.*, pain is irrelevant with respect to any other condition, *e.g.*, menopausal flushing.

Moreover, it has been reported that clonidine is effective in treating menopausal flushing, but not in treating rosacea flushing. Therefore, an ability of an alpha-adrenergic receptor agonist to treat one condition cannot be extrapolated to the treatment of another condition, even where flushing is a symptom of both conditions.

Summary of Unpredictability

In view of the above, therefore, a person of ordinary skill in the art would not be able to predict the effects of agonizing a particular alpha-adrenergic receptor. Applicant summarizes below some of the reasons for this unpredictability.

The examiner's primary reference in the obviousness rejection discloses that transdermal, *i.e.*, systemic, administration of clonidine is effective in treating menopausal flushing. However, it is not reasonable to expect that a different mode of administration, *i.e.* local administration, of a different compound, *i.e.*, brimonidine, would also be effective for the same purpose.

Shanler, et al., which is discussed above, acknowledges the unpredictability of the effects of alpha-adrenoreceptor agonists. In particular, Shanler, et al. discloses that the final local and systemic effects of an alpha-adrenoreceptor agonist are "myriad" and may include "effects ranging from vasoconstriction to vasodilation."

Furthermore, Gil, et al.'s invention speaks of the unpredictability in the art by including both an effective amount of an α-adrenergic agonist and a selective α-2A antagonist in their pharmaceutical composition to alleviate pain. See Gil, et al., paragraph 8.

Wymenga confirms the unpredictability of how flushing occurs by stating that "[t]he pathophysiology of flushes is not entirely elucidated." See Wymenga on page 270, last full sentence of first column.

Further evidence that clonidine and brimonidine are not functionally equivalent in their effects in treating a particular condition is the fact that the compounds are reported to differ in their ability to treat flushing associated with rosacea. Clonidine has been reported to be ineffective for treating flushing associated with rosacea. By contrast, brimonidine has been reported to be effective in treating flushing associated with rosacea. See the Response filed December 9, 2008, pages 5 and 6.

In view of the unexpected behavior of alpha-adrenergic receptor agonists, the examiner is respectfully requested to reconsider and withdraw the pending obviousness rejection.

For the foregoing reasons, applicant maintains that the unpredictability of the effects of alpha-adrenoreceptor agonists supports the patentability of the claimed invention.

Applicant respectfully submits that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the examiner contact applicant's attorney at the telephone number provided below.

Respectfully submitted,

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